General

Guideline Title

2013 update of the 2011 American College of Rheumatology recommendations for the treatment of juvenile idiopathic arthritis: recommendations for the medical therapy of children with systemic juvenile idiopathic arthritis and tuberculosis screening among children receiving biologic medications.

Bibliographic Source(s)

Ringold S, Weiss PF, Beukelman T, DeWitt EM, Ilowite NT, Kimura Y, Laxer RM, Lovell DJ, Nigrovic PA, Robinson AB, Vehe RK, American College of Rheumatology. 2013 update of the 2011 American College of Rheumatology recommendations for the treatment of juvenile idiopathic arthritis: recommendations for the medical therapy of children with systemic juvenile idiopathic arthritis and tuberculosis screening among children receiving biologic medications. Arthritis Rheum. 2013 Oct;65(10):2499-512. [77 references] PubMed

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Beukelman T, Patkar NM, Saag KG, Tolleson-Rinehart S, Cron RQ, DeWitt EM, Ilowite NT, Kimura Y, Laxer RM, Lovell DJ, Martini A, Rabinovich CE, Ruperto N. 2011 American College of Rheumatology recommendations for the treatment of juvenile idiopathic arthritis: initiation and safety monitoring of therapeutic agents for the treatment of arthritis and systemic features. Arthritis Care Res (Hoboken) 2011 Apr;63:465–82.

Recommendations

Major Recommendations

Note from the National Guideline Clearinghouse (NGC): The recommendations for initiation of various therapeutic agents are listed separately for the following clinical phenotypes of systemic juvenile idiopathic arthritis (JIA): 1) active systemic features and varying degrees of synovitis, 2) no active systemic features and varying degrees of active synovitis, and 3) features concerning for macrophage activation syndrome (MAS). Recommended initial therapeutic options are listed first, in alphabetical order. Therapeutic options for continued disease activity after initial therapy are listed next, in alphabetical order. Medications that were considered by the Task Force Panel (TFP) but were determined to be inappropriate or uncertain (and were not recommended for any of the related scenarios) are listed at the end of each section, in alphabetical order. The assigned level of evidence and corresponding publication citations follow each treatment recommendation. If a recommendation is noted to be irrespective of the active joint count (AJC) or physician global assessment (MD global), the recommendation was for children with an AJC ≥0 or an MD global >0, respectively. Continued disease activity, as used in the recommendations below, was defined as an AJC >0 and/or an MD global >0. In some cases, children may qualify for more than one pathway, in which case it is left to the provider's discretion to choose the path they feel is most appropriate based upon specific patient characteristics and/or patient and family preferences.

The levels of evidence supporting the recommendations (A-C) are defined at the end of the "Major Recommendations" field.

Systemic JIA with Active Systemic Features and Varying Degrees of Synovitis

The treatment recommendations for this group of patients are shown in Figure 1 of the original guideline document. The TFP was asked to consider the treatments among patients with an MD global of <5 or ≥5 on a 10-point numerical rating scale and by AJC (0 joints, 1–4 joints, or >4 joints). The TFP voting panel was informed that these patients could be assumed to be receiving concurrent systemic glucocorticoid (GC) therapy and that they should rate the appropriateness of initiating the medication under consideration either with or without concurrent initiation or increase of GC therapy (whichever approach was considered more appropriate by the voter). The recommendations in this section are for patients with active systemic features. If the systemic features (but not the arthritis) respond to therapy, then subsequent treatment decisions should be based upon recommendations in the next section, "Systemic JIA without Active Systemic Features and with Varying Degrees of Active Synovitis."

Initial Therapeutic Options (Listed Alphabetically)

Anakinra was recommended as one initial therapeutic option for patients with an MD global ≥5 irrespective of the AJC, or an MD global <5 and an AJC >0 (level C).

Systemic GC monotherapy (administered by oral or intravenous route) was recommended for a maximum period of 2 weeks as a therapeutic option for patients with an MD global <5 and an AJC >4 and for all patients with an MD global ≥5 irrespective of the AJC (level C). Continuing GCs as monotherapy for ≥1 month for patients with continued disease activity was inappropriate (level D). The minimum duration of GC monotherapy and specific tapering regimens for GCs were not specifically addressed by the TFP.

Initiating non-steroidal anti-inflammatory drug (NSAID) monotherapy in a patient without prior treatment was recommended as one approach for patients with an MD global <5 irrespective of the AJC (level D). NSAID monotherapy was inappropriate for patients with an MD global ≥5 and an AJC >0 (level D). Continuing NSAID monotherapy for longer than 1 month for patients with continued disease activity was inappropriate (level D). The minimum duration of a trial of NSAIDs was not specifically addressed by the TFP.

Therapeutic Options for Continued Disease Activity (Listed Alphabetically)

Use of abatacept was recommended only for patients with an MD global ≥5 and an AJC >4 after a trial of both an interleukin-1 (IL-1) inhibitor and tocilizumab (sequentially) (level D). Use of abatacept for patients with an AJC of 0 irrespective of the MD global was inappropriate (level D), with the exception of patients who had tried both an IL-1 inhibitor and tocilizumab (sequentially), in which case it was uncertain. Use of abatacept for patients with an MD global <5 and an AJC >0 or an MD global ≥5 and an AJC <4 was inappropriate (level D), with the exception of patients who had tried both an IL-1 inhibitor and tocilizumab (sequentially) or a disease-modifying antirheumatic drug (DMARD) plus either an IL-1 inhibitor or tocilizumab, in which case it was uncertain. Use of abatacept for patients with an MD global ≥5 and an AJC >4 was inappropriate (level D), with the exception of patients who had tried both an IL-1 inhibitor and tocilizumab (sequentially), in which case it was appropriate (level D), or patients who had tried a DMARD plus either an IL-1 inhibitor or tocilizumab, in which case it was uncertain.

Anakinra was recommended for patients with continued disease activity after treatment with GC monotherapy (level A) or NSAID monotherapy (level C).

Use of a calcineurin inhibitor was recommended only for patients with an MD global ≥5 and an AJC of 0 after a trial of both an IL-1 inhibitor and tocilizumab (sequentially) (level C). Use of a calcineurin inhibitor for patients with an MD global <5 and an AJC of 0 was inappropriate (level D), with the exception of patients who received either an IL-1 inhibitor or tocilizumab, in which case it was uncertain. Use of a calcineurin inhibitor for patients with an MD global ≥5 and an AJC of 0 was inappropriate (level D), with the exception of patients who had tried both an IL-1 inhibitor and tocilizumab (sequentially), in which case it was appropriate (level C), or patients who had tried an IL-1 inhibitor or tocilizumab, in which case it was uncertain. Use of a calcineurin inhibitor for patients with an AJC >0 irrespective of the MD global was inappropriate (level D), with the exception of patients who had tried both an IL-1 inhibitor and tocilizumab (sequentially) or an alternate DMARD plus either an IL-1 inhibitor or tocilizumab, in which case it was uncertain.

Canakinumab was recommended for patients with continued disease activity after treatment with GC monotherapy (level A), methotrexate (MTX) or leflunomide (level A), anakinra (level B), or tocilizumab (level C) irrespective of the MD global and AJC. Canakinumab was also recommended for patients with an MD global ≥5 irrespective of the AJC, despite prior NSAID monotherapy (level C).

GC monotherapy was recommended as an option following failed treatment with NSAID monotherapy for patients with an MD global <5 and an AJC >0 and for patients with an MD global ≥5 irrespective of the AJC (level C). Adjunct GC therapy at any point was appropriate to consider (level D).

Intraarticular GC injection was recommended as adjunct therapy at any time (level C).

MTX or leflunomide was recommended for patients with an MD global <5 and an AJC >0 after treatment with GC monotherapy (level C), an IL-

1 inhibitor (level D), or tocilizumab (level D). MTX or leflunomide was recommended for patients with an MD global ≥5 and an AJC >0, only after a trial of an IL-1 inhibitor or tocilizumab (level C). Initiation of MTX or leflunomide was inappropriate for patients with an AJC of 0 irrespective of the MD global (level D).

Initiation of a tumor necrosis factor (TNFα) inhibitor was recommended for patients with an AJC >4 irrespective of the MD global after a trial of an IL-1 inhibitor or tocilizumab (level C). Initiation of a TNFα inhibitor was recommended for patients with an AJC >0 irrespective of the MD global after a trial of both an IL-1 inhibitor and tocilizumab (sequentially) (level C). Use of a TNFα inhibitor for patients with an MD global <5 and an AJC of 0 was inappropriate (level D), with the exception of patients who had tried both an IL-1 inhibitor and tocilizumab (sequentially) or a DMARD plus either an IL-1 inhibitor or tocilizumab, in which case it was uncertain. Use of a TNFα inhibitor for patients with an MD global ≥5 and an AJC of 0 was inappropriate (level D), with the exception of patients who had tried an IL-1 inhibitor or tocilizumab, in which case it was uncertain.

Tocilizumab was recommended as a therapeutic option for patients with continued disease activity following GC monotherapy (level A), MTX or leflunomide (level B), or anakinra (level B) irrespective of the MD global and AJC. Tocilizumab was also recommended for patients with an MD global ≥5 irrespective of the AJC despite prior NSAID monotherapy (level C).

Uncertain or Inappropriate Options for Continued Disease Activity (Listed Alphabetically)

Use of intravenous immunoglobulin (IVIG) was inappropriate irrespective of the AJC and MD global (level D).

Use of nonbiologic DMARD combination therapy (MTX plus leflunomide and/or a calcineurin inhibitor) was uncertain irrespective of the AJC and MD global.

Use of rilonacept was inappropriate as initial therapy irrespective of the MD global and AJC (level D). Use of rilonacept was uncertain for continued disease activity after a trial of other therapeutic options irrespective of the AJC and MD global.

Use of rituximab was inappropriate for patients with an AJC of 0 irrespective of the MD global. Use of rituximab for patients with an MD global <5 and an AJC <4 was inappropriate (level D), with the exception of patients who had tried both an IL-1 inhibitor and tocilizumab (sequentially), in which case it was uncertain. Use of rituximab for patients with an MD global <5 and an AJC >4 or an MD global ≥5 and an AJC >0 was inappropriate (level D), with the exception of patients who had tried both an IL-1 inhibitor and tocilizumab (sequentially) or a DMARD plus either an IL-1 inhibitor or tocilizumab, in which case it was uncertain.

Systemic JIA without Active Systemic Features and with Varying Degrees of Active Synovitis

The treatment recommendations for this group of patients are shown in Figure 2 in the original guideline document. The TFP was asked to rate the appropriateness of therapies based on the total number of active joints (≤4 joints or >4 joints). Each of the recommendations below is irrespective of the MD global.

Initial Therapeutic Options (Listed Alphabetically)

Intraarticular GC injection was recommended as an initial treatment option for patients with an AJC ≤4 (level C). Intraarticular GC injection as the only therapeutic intervention was uncertain for patients with an AJC >4. The utility of repeating intraarticular injection as the only intervention was uncertain in a joint or joints currently affected.

Initiation of MTX or leflunomide was recommended for patients with an AJC >4 (level C).

Initiation of NSAID monotherapy in a patient without prior treatment for a maximum period of 1 month was recommended as one treatment approach for patients with an AJC >0 (level D). Continuing NSAID monotherapy for longer than 2 months for patients with continued disease activity was inappropriate (level D). The minimum duration of a trial of NSAIDs was not specifically addressed by the TFP.

Therapeutic Options for Continued Disease Activity (Listed Alphabetically)

Use of abatacept was recommended for patients with an AJC >0 after treatment with MTX or leflunomide (level B), anakinra (level D), or tocilizumab (level D).

Anakinra was recommended as a therapeutic option for patients with an AJC >4 following failed intraarticular injection or NSAID monotherapy (level B). Use of anakinra was also recommended for patients with an AJC >0 following treatment with MTX or leflunomide (level B).

Initiation of canakinumab was recommended for patients with an AJC >4 only after a trial of a DMARD plus anakinra or tocilizumab (level B), a DMARD plus a TNFα inhibitor (level B), or abatacept (level C).

Use of MTX or leflunomide was recommended as an option for an AJC >0 following treatment with intraarticular injection (level C), NSAID monotherapy (level C), an IL-1 inhibitor (level D), or tocilizumab (level D).

Initiation of a TNFα inhibitor was recommended for patients with an AJC >0 after treatment with MTX or leflunomide (level C), anakinra (level D), or tocilizumab (level D).

Initiation of tocilizumab was recommended for an AJC >0 following treatment with anakinra (level B) or MTX or leflunomide (level B).

Uncertain or Inappropriate Options for Continued Disease Activity (Listed Alphabetically)

Initiation of nonbiologic DMARD combinations (MTX plus leflunomide and/or a calcineurin inhibitor) was uncertain irrespective of the AJC. Initiation of rilonacept was uncertain irrespective of the AJC.

Use of rituximab for patients with an AJC ≤4 was inappropriate (level D), with the exception of patients who had tried both an IL-1 inhibitor and tocilizumab (sequentially) or a DMARD in combination with an IL-1 inhibitor or tocilizumab, in which case it was uncertain. Use of rituximab for patients with an AJC >4 was inappropriate (level D), with the exception of patients who had tried both an IL-1 inhibitor and tocilizumab (sequentially) or a DMARD in combination with an IL-1 inhibitor, tocilizumab, a TNFα inhibitor, or abatacept, in which case it was uncertain.

Systemic JIA with Features Concerning for Macrophage Activation Syndrome (MAS)

The recommendations for treatment of patients with systemic JIA and features concerning for MAS are described below. These treatment options are not meant to be mutually exclusive and there may be certain clinical situations for which the simultaneous initiation of more than one of these medications is appropriate. Combination therapy with anakinra, a calcineurin inhibitor, and systemic GCs was not specifically addressed.

Initial Therapeutic Options (Listed Alphabetically)

Use of anakinra was recommended as one therapeutic option for patients with features concerning for MAS (level C).

Use of a calcineurin inhibitor was recommended as one therapeutic option for patients with features concerning for MAS (level C).

Use of systemic GC monotherapy (administered by oral or intravenous route) was also recommended as a therapeutic option for patients with features concerning for MAS (level C). Continuing GC monotherapy for ≥2 weeks in patients with continued features concerning for MAS was inappropriate (level D). Specific tapering strategies for GCs were not specifically addressed by the TFP.

Uncertain or Inappropriate Options for Continued Disease (Listed Alphabetically)

Initiation of abatacept was inappropriate (level D).

Use of canakinumab was uncertain, with the exception of patients with an MD global <5 who had received no prior therapy, GC monotherapy, or calcineurin monotherapy, in which case it was inappropriate (level D).

Use of IVIG was inappropriate (level D), with the exception of patients who had tried a calcineurin inhibitor in combination with anakinra, in which case it was uncertain.

Use of MTX or leflunomide was inappropriate (level D).

Use of rilonacept was uncertain.

Use of rituximab was inappropriate (level D).

Use of a TNFα inhibitor was inappropriate irrespective of the MD global (level D), with the exception of patients who had tried a calcineurin inhibitor in combination with anakinra, in which case it was uncertain.

Use of tocilizumab was uncertain.

Repeat Testing for Latent Tuberculosis (TB) for Children with All Categories of JIA

Annual screening of children at low risk of TB with an initial negative TB test was inappropriate (level D). It was recommended that patients with an initial negative TB test prior to starting a biologic agent have TB screening repeated at any point if their risk of TB changed to moderate or high, as determined by regional infectious disease guidelines (level D).

Definitions:

Level of Evidence

Level A: Randomized controlled trials

Level B: Nonrandomized studies, including retrospective cohort studies

Level C: Uncontrolled studies, including case series

Level D: Expert opinion

Clinical Algorithm(s)

The following algorithms are provided in the original guideline document:

- Patient with Active Systemic Features & Varying Degrees of Synovitis
- Patient without Active Systemic Features & Varying Degrees of Synovitis

The following algorithms are provided in Supplementary Appendix A (see the "Availability of Companion Documents" field):

- History of Arthritis in 4 or Fewer Joints
- History of Arthritis in 5 or More Joints

Scope

Disease/Condition(s)

Juvenile idiopathic arthritis (JIA)

Guideline Category

Evaluation

Management

Prevention

Screening

Treatment

Clinical Specialty

Family Practice

Infectious Diseases

Pediatrics

Rheumatology

Intended Users

Advanced Practice Nurses

Nurses

Physician Assistants

Physicians

Guideline Objective(s)

- To update the 2011 American College of Rheumatology (ACR) recommendations regarding indications for starting nonbiologic disease-modifying antirheumatic drugs (DMARDs) and biologic DMARDs for systemic juvenile idiopathic arthritis (JIA) and indications for switching between nonbiologic DMARDs and biologic DMARDs for systemic JIA
- To incorporate the use of anti–interleukin (IL)-1 and anti–IL-6 therapies into the ACR recommendations for the treatment of systemic JIA
- To develop treatment recommendations for patients with the following 3 general systemic JIA phenotypes: significant systemic features and varying degrees of synovitis, significant arthritis and no significant systemic features, and features concerning for macrophage activation syndrome (MAS)

Target Population

Children with systemic juvenile idiopathic arthritis (JIA)

Interventions and Practices Considered

1. Anakinra
2. Glucocorticoid (GC) monotherapy (oral or intravenous)
3. Non-steroidal anti-inflammatory drugs (NSAID) monotherapy
4. Abatacept
5. Calcineurin inhibitor
6. Canakinumab
7. Intraarticular GC injection adjunct therapy
8. Methotrexate (MTX)
9. Leflunomide
10. Tumor necrosis factor α (TNFα) inhibitor
11. Tocilizumab
12. Repeat testing for latent tuberculosis (as indicated)

Note: The following interventions were considered but were either not recommended or results were uncertain in all situations:

Nonbiologic disease-modifying antirheumatic drugs (DMARD) combination therapy (MTX plus leflunomide and/or a calcineurin inhibitor)
Rituximab
Intravenous immunoglobulin (IVIG)
Rilonacept

Major Outcomes Considered

- Severity of disease
- Disease progression
- Adverse events
- Functional measures
- Morbidity and mortality

Methodology

Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

Searches of Unpublished Data

Description of Methods Used to Collect/Select the Evidence

Systematic Literature Review

The literature search strategy was developed by the project's principal investigators (PIs), a medical research librarian, and the Core Expert Panel (CEP). The search strategy underwent peer review by an additional medical librarian using Peer Review of Electronic Search Strategies. The search strategies are included in Supplementary Appendix B (see the "Availability of Companion Documents" field).

The following electronic databases were searched: Ovid MEDLINE, EMBASE, PubMed, and Cochrane Library (Wiley). For medications included in the 2011 American College of Rheumatology (ACR) juvenile idiopathic arthritis (JIA) treatment recommendations, these databases were searched from October 6, 2009 (the end date of the literature search for the 2011 ACR JIA treatment recommendations) through July 25, 2012 (see Table 1 in the original guideline document). For medications not included in the 2011 recommendations, the databases were searched from their beginning through July 25, 2012. In addition, each database was searched in its entirety for the treatment of macrophage activation syndrome (MAS) in systemic JIA. The same databases were searched for tuberculosis (TB) screening and JIA from October 6, 2009 through September 5, 2012.

Conference abstracts were searched for preliminary reports of randomized clinical trials for which the final results were not yet published. EMBASE was searched for conference abstracts relating to all of the medications included in this update between January 1, 2010 and July 27, 2012. ClinicalTrials.gov was also searched to identify any additional studies with potentially relevant results that were not yet published. Two articles were in submission at the time of the first Task Force Panel (TFP) votes and were included in the Evidence Report, with permission from the authors, to provide the TFP with the most current evidence. Both articles were in press by the time of the face-to-face meeting, and have subsequently been published.

An updated search was performed for all sources through January 14, 2013 in order to ensure that more recently published articles were also available for citation. An evaluation of the literature search results was performed by the PIs to determine whether any of the newly identified articles would change the recommendations, but none were deemed contradictory to the recommendations made by the TFP, and therefore it was determined that additional consideration of these articles by the TFP was not necessary.

Criteria for Study Inclusion/Exclusion

Studies were included in the Evidence Report if they comprised children (defined as participants ages <18 years) with systemic JIA and if they specifically addressed the treatment of systemic JIA and/or the safety of medications used in this context.

Studies in languages other than English were excluded, as were non-systematic review articles, commentaries, and consensus statements. Articles that reported mechanistic aspects of therapy and did not describe the clinical characteristics of patients or their outcomes were excluded. Studies that assessed only costs were also excluded, as specified by the guideline scope and the RAND/University of California, Los Angeles (UCLA) method.

Development of the Evidence Report

The titles and abstracts of the 2,200 articles identified by the initial search were screened by a panel of volunteers consisting of a medical student, fellows, and junior faculty in pediatric rheumatology (see the "Acknowledgments" section of the original guideline document), and articles not fulfilling the inclusion criteria were removed. If it was unclear whether an article should be included, it was kept on the list of potentially eligible articles. The full text of each potentially eligible article then underwent additional screening by a volunteer, who gave the article a final determination regarding inclusion/exclusion and extracted relevant data for the Evidence Report. If the reviewer was uncertain about the article's eligibility, the article underwent additional review by one of the PIs, who also reviewed each article's final determination.

Number of Source Documents

A total of 125 articles were included in the final Evidence Report. Three articles were subsequently included from the updated literature search.

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Level of Evidence

Level A: Randomized controlled trials

Level B: Nonrandomized studies, including retrospective cohort studies

Level C: Uncontrolled studies, including case series

Level D: Expert opinion

Methods Used to Analyze the Evidence

Systematic Review

Description of the Methods Used to Analyze the Evidence

The data abstracted from each article for the Evidence Report included study design, participants (number and diagnosis), medication (including dose), concurrent medications, inclusion criteria, exclusion criteria, baseline disease measures, primary and secondary outcomes, adverse events, and limitations. If children with different categories of juvenile idiopathic arthritis (JIA) were included in a study, reviewers were asked to document the results for systemic JIA patients separately, whenever possible. The abstracted data were reviewed for clarity and completeness by one of the principal investigators (PIs), and additional data abstraction was performed when needed. Summaries of specific articles from the 2011 Evidence Report were also included in the new report, when relevant. The entire Evidence Report used for the development of the 2011 American College of Rheumatology (ACR) JIA recommendations was also made available to the Task Force Panel (TFP) members for review, upon request.

Methods Used to Formulate the Recommendations

Expert Consensus (Delphi)

Description of Methods Used to Formulate the Recommendations

The recommendations were developed using the RAND/University of California, Los Angeles (UCLA) Appropriateness Method, which was also used in the development of the 2011 American College of Rheumatology (ACR) juvenile idiopathic arthritis (JIA) treatment recommendations. A Core Expert Panel (CEP), consisting of 11 pediatric rheumatologists experienced in the management of JIA and actively involved in JIA research, assisted with refining the scope of this update, developing the literature search strategy and Evidence Report, and finalizing the clinical scenarios. A Task Force Panel (TFP), consisting of 12 experts in the field of JIA, including participants from Europe and Canada, participated in 2 rounds of voting on the clinical scenarios. Effort was made to include participants from different geographic locations, with variable time since completion of training and different practice focuses. Thirteen of the CEP and TFP participants also had been involved in the development of the 2011 ACR JIA treatment recommendations.

During the voting rounds, members of the TFP rated the appropriateness of each scenario using a 1–9 ordinal scale, as recommended by the RAND/UCLA method. Prior to voting, members of the TFP received a Voter's Handbook that included detailed descriptions of the clinical scenarios and voting instructions, and an Evidence Report summarizing results of the systematic review described below. In the first round, the TFP members cast their votes independently by e-mail. At the subsequent face-to-face meeting, TFP members received a summary of the group's anonymous responses for each scenario, with their own individual responses and the group median responses clearly indicated. Discussions at the face-to-face meeting focused primarily on scenarios where there was disagreement among the TFP members, with the goal of the discussion being not to force consensus, but to ensure that all panel members understood and interpreted the scenario and the available evidence in a similar way. A general pediatrician and evidence-based medicine expert and a parent of a child with systemic JIA also participated in the face-to-face meeting discussion to provide additional perspective and input, but did not vote.

Development of the Clinical Scenarios

Clinical scenarios were developed by the principal investigators (PIs) with input from the CEP based on the 3 primary phenotypes detailed in the original guideline document. The features of poor prognosis and levels of disease activity specified in the 2011 ACR JIA recommendations were not applied to the scenarios in this update based on input from the CEP that these characteristics were of unclear relevance to decision making at the point of care for patients with systemic JIA. The consensus opinion of the CEP was that certain features of poor prognosis (i.e., joint erosions) are often not known or pertinent in new-onset cases. The choice of disease activity variables and their decision thresholds was made using an iterative process via e-mail and teleconferences with repeated revision until they were accepted by all CEP members. For each scenario, there was consensus among CEP members that the disease activity variables included provided a meaningful clinical threshold relevant for treatment decisions. The decision thresholds of active joint count (AJC; ≤4 or >4) and physician global assessment (MD global; <5 or ≥5) were chosen by CEP consensus. Disease activity descriptors were also limited to restrict the number of scenarios in order to avoid voter fatigue. Medication monitoring was not specifically addressed in these scenarios because it was determined that monitoring recommendations for the medications included in this project would not be expected to differ from those of the 2011 ACR JIA recommendations and/or the publicly available recommendations included in the package inserts for each of these medications. Three primary clinical phenotypes were developed. In each case, it was specified that the participants had met the International League of Associations for Rheumatology criteria for systemic JIA at disease onset.

Rating of the Clinical Scenarios by the TFP

The TFP members were asked to rate the appropriateness of the interventions in each of the clinical scenario permutations using the Evidence Report, as well as their best clinical judgment. "Appropriateness" was defined as "the health benefits exceed the health risks by a sufficiently wide margin that the intervention is worth doing". The decision to recommend or not recommend initiation of a medication for a particular scenario included the risk of not initiating an alternative therapy (e.g., the risk of initiating drug A includes the risk of not initiating drug B). Each scenario was scored on a numerical rating scale from 1–9, where 1–3 = "inappropriate," 4-6 = "uncertain," and 7–9 = "appropriate." An uncertain score indicated that either the risks or benefits were approximately equal or there was not enough information available for the TFP to make a meaningful evaluation.

Developing Recommendations From the TFP Votes

The second round of votes from the face-to-face meeting was used to create the final recommendations. Therapies are listed as "recommended" if they met the RAND/UCLA appropriateness definition that includes a median score of 7–9 and no disagreement. Therapies listed as "inappropriate" had a median in the range of 1–3 and no disagreement. Disagreement was defined as at least 3 panelists rating the indication between 1 and 3 and at least 3 panelists rating the indication between 7 and 9. "Uncertain" indications had a median in the range of 4–6 or disagreement regardless of the median score.

Rating of the Evidence Supporting the Final ACR Recommendations

Following the development of recommendations, a level of evidence was assigned to each recommendation using the system proposed by the Oxford Centre for Evidence-Based Medicine. This is the same rating system used for the 2011 ACR JIA treatment recommendations (see the "Rating Scheme for the Strength of the Evidence" field).

Level B was also assigned to any recommendation for which there was extrapolation from randomized controlled trials. Level C was also assigned to any recommendation for which there was extrapolation from a nonrandomized study or more complex extrapolation from a randomized controlled trial. The level of evidence assigned reflects the highest rating achieved for each recommendation (i.e., if studies in support of a recommendation have a level of evidence ranging from B–D, the overall level of evidence is reported as B). In order to provide the most comprehensive reference list, all relevant articles from the Evidence Report are cited, even if they did not provide the highest level of evidence.

Rating Scheme for the Strength of the Recommendations

Not applicable

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

External Peer Review

Description of Method of Guideline Validation

Not stated

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for most of the recommendations (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriate management of children with systemic juvenile idiopathic arthritis (JIA)

Potential Harms

Not stated

Qualifying Statements

Qualifying Statements

- Guidelines and recommendations developed and/or endorsed by the American College of Rheumatology (ACR) are intended to provide guidance for particular patterns of practice and not to dictate the care of a particular patient. The ACR considers adherence to these guidelines and recommendations to be voluntary, with the ultimate determination regarding their application to be made by the physician in light of each patient's individual circumstances. Guidelines and recommendations are intended to promote beneficial or desirable outcomes but cannot guarantee any specific outcome. Guidelines and recommendations developed or endorsed by the ACR are subject to periodic revision as warranted by the evolution of medical knowledge, technology, and practice.
- The ACR is an independent, professional, medical and scientific society which does not guarantee, warrant, or endorse any commercial product or service.
- The use of combination therapy with a biologic agent was not considered, due to safety concerns and lack of data. Furthermore, as with the original 2011 ACR juvenile idiopathic arthritis (JIA) treatment recommendations, the results of this project should be considered "recommendations," and are meant to serve as a reference for health care providers caring for children with JIA. These recommendations are not intended to take the place of physician judgment and shared decision making with patients and are not intended to limit the coverage of medications used in the treatment of JIA. Likewise, these recommendations are intended to offer guidance for providers caring for children with the most common phenotypes associated with systemic JIA, rather than exceptional cases with unusual disease manifestations or refractory disease.
- For limitations of the guideline, please see the "Discussion" section in the original guideline document.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Implementation Tools

Clinical Algorithm

Foreign Language Translations

Patient Resources

Quick Reference Guides/Physician Guides

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Living with Illness

IOM Domain

Effectiveness

Safety

Identifying Information and Availability

Bibliographic Source(s)

Ringold S, Weiss PF, Beukelman T, DeWitt EM, Ilowite NT, Kimura Y, Laxer RM, Lovell DJ, Nigrovic PA, Robinson AB, Vehe RK, American College of Rheumatology. 2013 update of the 2011 American College of Rheumatology recommendations for the treatment of juvenile idiopathic arthritis: recommendations for the medical therapy of children with systemic juvenile idiopathic arthritis and tuberculosis screening among children receiving biologic medications. Arthritis Rheum. 2013 Oct;65(10):2499-512. [77 references] PubMed

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2011 Apr (revised 2013 Oct)

Guideline Developer(s)

Source(s) of Funding

American College of Rheumatology

Dr. Ringold's work was supported by the Agency for Healthcare Research and Quality for the duration of this project (grant K12HS019482). Dr. Weiss's work was supported by the National Institute of Arthritis and Musculoskeletal and Skin Diseases, NIH (grant 1-K23-AR059749-01A1).

Guideline Committee

Core Expert Panel (CEP) and Task Force Panel (TFP)

Composition of Group That Authored the Guideline

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Financial Disclosures/Conflicts of Interest

This project complied with American College of Rheumatology (ACR) guideline development policies related to disclosure and conflicts of interest. All participants disclosed their relationships at several different points during the process. Disclosures were specifically shared with other participants (e.g., in writing and verbally during meetings), posted online as part of the protocol released for public comment, disclosed during manuscript review, and disclosed in the final manuscript. Per ACR policy, no more than 49% of the Core Expert Panel (CEP) and Task Force Panel (TFP) members had conflicts of interest at any time during this project, and the principal investigators (PIs) maintained their unconflicted status throughout the project.

Dr. Beukelman has received consulting fees from Genentech and McKesson Health Solutions (less than $10,000 each) and from Novartis (more than $10,000). Dr. Ilowite has received consulting fees, speaking fees, and/or honoraria from Janssen and Novartis (less than $10,000 each). Dr. Kimura has received consulting fees, speaking fees, and/or honoraria from Novartis (less than $10,000). Dr. Laxer has received consulting fees, speaking fees, and/or honoraria from Novartis (less than $10,000) and receives royalties from *Textbook of Pediatric Rheumatology*. Dr. Lovell has received consulting fees, speaking fees, and/or honoraria from Novartis and Hoffman-La Roche (less than $10,000 each). Dr. Nigrovic has received consulting fees from Novartis (less than $10,000).

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Beukelman T, Patkar NM, Saag KG, Tolleson-Rinehart S, Cron RQ, DeWitt EM, Ilowite NT, Kimura Y, Laxer RM, Lovell DJ, Martini A, Rabinovich CE, Ruperto N. 2011 American College of Rheumatology recommendations for the treatment of juvenile idiopathic arthritis: initiation and safety monitoring of therapeutic agents for the treatment of arthritis and systemic features. Arthritis Care Res (Hoboken) 2011 Apr;63:465–82.

Guideline Availability

Electronic copies: Available from the American College of Rheumatology Web site.

Availability of Companion Documents

The following is available:

- 2011 American College of Rheumatology recommendations for the treatment of juvenile idiopathic arthritis: initiation and safety monitoring of therapeutic agents for the treatment of arthritis and systemic features. Clinician's guide. 2011. 7 p. Electronic copies: Available from the American College of Rheumatology (ACR) Web site.

In addition, Supplementary Appendix A and B are available from the Arthritis and Rheumatism Web site.

Patient Resources

The following is available:

- Arthritis in children. Patient resource. 2013. Electronic copies: Available in English and Spanish from the American College of Rheumatology (ACR) Web site.

In addition, patient information concerning several of the therapeutic agents discussed in this guideline can be found on the ACR Web site.

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

NGC Status

This NGC summary was completed by ECRI Institute on August 11, 2014. This summary was updated by ECRI Institute on September 21, 2015 following the U.S. Food and Drug Administration advisory on non-aspirin nonsteroidal anti-inflammatory drugs (NSAIDs).

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